BMJ

LONDON, SATURDAY 16 JULY 1994

Chernobyl, childhood cancer, and chromosome 21

Probably nothing to worry about

See papers on p 151, p154 and p158

In 1986 the accident at the nuclear reactor in Chernobyl in the former Soviet Union released large amounts of radioactivity into the atmosphere. Adjacent areas were heavily contaminated, while more distant regions were affected less. International committees concluded that valuable information on the effects of radiation might result from long term follow up of workers affected by the accident, many of whom received doses in the range of 250-1000 mSv. The committees also recommended that studies should be carried out of residents living within a 30 km radius of the reactor and of residents of substantially contaminated regions in Belarus, the Ukraine, and Russia, who may have received doses of 50-60 mSv. The scientific value of investigations in Europe and other parts of the former Soviet Union was questioned, however, because estimated exposures (<1 mSv) were believed to have been too low to cause a detectable excess of cases of cancer or genetic defects.[1] For comparison, annual doses from natural background radiation are 1-2 mSv.[2]

Nevertheless, because of widespread concern among populations in Europe living in areas of low fallout, the International Agency for Research on Cancer organised the European childhood leukaemia-lymphoma incidence study using population based cancer registries in 20 countries. Preliminary results at the end of 1988 showed no increase in childhood leukaemia, but the follow up was probably too short.[3] Results of extended follow up of cancer registries to the end of 1992 in two countries participating in the European study, Finland and Sweden, are published in this week's journal (p 151, p 154)[4,5] and essentially report negative results, similar to those of a recent study of heavily contaminated regions in Belarus.[6]

While these reports may calm public anxieties, such descriptive (ecological) studies are inherently limited. Ecological studies focus on groups rather than individuals as the unit of observation and evaluate variations in the distribution of disease over geographical regions or time. Because exposures cannot be correlated with disease in the same person and because confounding factors cannot be adequately controlled for, such studies are especially prone to bias.[7] Thus, higher rates of cancer in regions with greater radiation contamination cannot be ascribed with certainty to the exposure related to the accident.[8] Ecological studies are useful for generating hypotheses but are of limited value in testing hypotheses or quantifying risks of cancer associated with environmental exposures.

Studies of low doses also have limited statistical power to detect effects.[9] Although radiation can cause leukaemia, our accumulated knowledge would lead us to conclude beforehand that the tiny doses received in Scandinavia were much too small for an excess of cases to be expected.[1] Even in Finland the estimated dose of radiation from Chernobyl was only 0.4 mSv,[4] whereas the estimated cumulative natural background dose was 6-12 mSv during 1987-92. While the absence of an effect from radiation is unsurprising, the wide confidence intervals preclude the rejection of the small effect predicted because of the low doses involved. Paradoxically, if a significant result was found at such low doses our cumulative experience with cancer related to radiation might lead us to treat the observation as a chance (or biased) occurrence.[9]

A third ecological study in this week's journal describes an apparent cluster of cases of Down's syndrome in Berlin, based on two cases that were diagnosed prenatally and 10 cases that were diagnosed in newborn infants, which occurred about nine months after the accident at Chernobyl (p 158).[10] An earlier report of this finding was previously criticised,[1] and this finding was not confirmed in subsequent larger and more representative series in Europe.[11] The authors dismiss too easily or fail to consider other explanations and several possible sources of bias. The effects of increased medical surveillance (shown by the notably sharper increase in prenatal diagnoses between 1986 and 1987 than in earlier or later periods) and possible reporting biases after the accident at Chernobyl are not discussed. The disproportionate occurrence of Down's syndrome among males in the Berlin study is peculiar since preconceptional radiation might be expected to reduce the number of male offspring. Trisomy 21 is significantly associated with maternal age, but no adjustment for this was made in the analysis. Furthermore, it is improbable that the very low doses in Berlin would result in a detectable excess while the higher doses in other parts of Europe did not.[11] The Berlin study is also inconsistent with studies of children of Japanese survivors of the atomic bombs, in whom no genetic anomalies, including Down's syndrome, were found in excess.[12] Analytical epidemiological studies of high dose maternal irradiation before conception are also equivocal.[2]

The special difficulties in evaluating ecological findings are further exemplified in a recent survey in Norway in which the risk of Down's syndrome fell with increasing levels of estimated radiation from Chernobyl.[13] Because misclassification of exposure and inadequate control of important cofactors can lead to spurious associations, both positive and negative, ecological analyses must be interpreted with great caution.

The importance of studies of human populations exposed to radiation from Chernobyl is not to prove that radiation causes cancer: this has been accepted for more than 50 years, and risks are remarkably well quantified.[2] Rather, the studies with individual dose characterisations might provide new information on the effects of exposure accumulated over several months to years, as compared with the instantaneous exposure received by the survivors of the atomic bombs in Japan. Studies of thyroid cancer in children exposed to iodine-131 might also contribute new knowledge. Cohort and case-control studies of workers and of populations living near Chernobyl remain the most promising way of obtaining quantitative information on the health risks from the accident.

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Recent developments in the drug treatment of motor neurone disease

Nothing works yet; many potential treatments remain uninvestigated

Motor neurone disease is a progressive degenerative disease of motor neurones leading to incapacitating neurological disability and death in over 1000 adults in Britain each year. About 5% of cases are familial; no specific treatment exists. The average length of survival from the onset of symptoms is only three years.

A recently reported controlled trial of riluzole, which inhibits release of glutamate,[1] in the treatment of motor neurone disease (known as amyotrophic lateral sclerosis in the United States) raised patients' hopes. It concluded that riluzole slightly slowed the fall in muscle strength and increased survival at one year in a small subgroup of patients.[2] Unfortunately, the overall results are not convincing of a significant benefit on a number of statistical and methodological grounds, and the findings of a larger, international trial are awaited.

The precise cause of motor neurone disease remains unknown. Excitotoxicity, oxidative stress, growth factors, and immunological abnormalities have all been included in pathogenetic theories, and current therapeutic trials are based on these concepts. The excitotoxic theory proposes that excess excitatory neurotransmitters, especially glutamate, lead to neural death and degeneration.[3] This has led to trials of branched chain amino acids in the condition. These amino acids activate glutamate dehydrogenase, an enzyme involved in the metabolism of glutamate, and it was believed that increasing the activity of this enzyme might reduce the putative neurotoxicity of glutamate. Although a pilot trial suggested benefit,[4] subsequent trials have not confirmed this.[5,6] The results of a multicentre European study collaboration (Scientific Pan-European Collaboration in Amyotrophic Lateral Sclerosis) are awaited. Lamotrigine, another inhibitor of the release of glutamate, prescribable in Britain for epilepsy, showed no beneficial effect in motor neurone disease in a controlled trial.[7] A pilot trial of dextromethorphan, an antagonist of glutamate receptors, also showed no benefit.[8] L-Threonine, a precursor of the inhibitory amino acid neurotransmitter glycine, has been reported to benefit spasticity in multiple sclerosis but did not benefit patients with motor neurone disease.[9]

Oxidative stress, including neurotoxicity mediated by free radicals, is a mechanism proposed for several neurodegenerative diseases, including Parkinson's disease.[10] The discovery of mutations in the gene for copper zinc superoxide dismutase, a scavenger of free radicals, in a minority of patients with familial motor neurone disease has supported the concept of oxidative stress.[11] The activity of this enzyme is reduced in these patients' erythrocytes,[12] but how a deficiency of such a ubiquitous enzyme could result in a neurodegenerative disease largely confined to motor neurones is uncertain. This observation, however, has raised hopes for treatment with antioxidants in some forms of familial motor neurone disease. Available antioxidants include selegiline (used in Parkinson's disease), vitamin C, vitamin E, and bromocriptine, although their value in motor neurone disease has not been established.

Several growth factors have been shown in vitro to prolong survival of motor neurones and promote growth of